REMARKS

Upon entry of the present amendment, claims 1 and 8-15 are pending in the above-referenced patent application and are currently under examination. Claims 2-7 and 16-28 have previously been canceled. Reconsideration of the application is respectfully requested.

Applicants acknowledge withdrawal of rejections under 35 U.S.C. §§ 112, 1st paragraph, 112, 2d paragraph and 102(b).

I. REJECTION UNDER 35 U.S.C. § 103(a) OVER DRISCOLL, WIERENGA AND MEYER

Claims 1 and 8-15 have been rejected under 35 USC § 103(a) as allegedly being obvious over Driscoll *et al.* in combination with Wierenga in view of Meyer *et al.* Applicants respectfully traverse the rejection in view of the comments below.

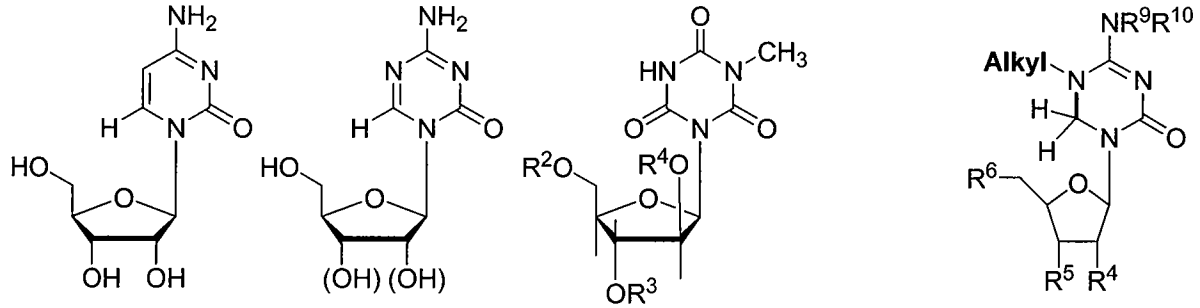
A claim is considered obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains" (35 USC § 103(a)). In order for the claims of the instant application to be obvious in view of the cited art, the prior art reference (or combination of references) must (1) teach or suggest the claim elements; (2) provide some suggestion or motivation to modify the reference in order to teach all of the elements; and (3) provide a reasonable expectation of success of making a compound of the instant application (MPEP § 2143). As discussed in detail below, none of the cited references satisfies all three requirements under MPEP § 2143.

The Examiner asserts that one of skill in the art, starting from the compounds of Driscoll *et al.*, would arrive at the compounds of the present invention through **routine experimentation** (Page 3, Final Office Action). Applicants respectfully disagree.

The test for obviousness was recently addressed in *KSR Int'l Co. v. Teleflex Inc.*, U.S., 127 S. Ct. 1727, 2007 WL 1237837 (2007), where the court cautioned against using a rigid approach . "The combination of familiar elements according to known methods is likely to be

obvious when it does no more than yield predictable results." KSR, 127 S. Ct. 1727, 2007 WL 1237837, at 12. However, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 127 S. Ct. 1727, 2007 WL 1237837, at 14.

The nucleosides of Driscoll *et al.* and Wierenga are cytidine analogs. Cytidine (see structure below) is characterized by having a 4-amino-pyrimidin-2-one ring linked to a ribofuranose. The pyrimidine ring has two ring nitrogens, and is *aromatic* as a result of unsaturation at the 3,4- and 5,6-positions, and the 1-aza and 2-carbonyl moieties. The compounds of Driscoll *et al.* and Wierenga are cytidine analogs. Instead of a pyrimidine ring, Driscoll *et al.* and Wierenga use a triazine ring. As for cytidine, the triazines of Driscoll *et al.* are *aromatic* as a result of unsaturation at the 3,4- and 5,6-positions, and the 1-aza and 2-carbonyl that provide the necessary additional conjugation. The triazine ring of Wierenga is also *aromatic*, despite the lack of any double-bonds in the triazine ring. The Wierenga triazine ring is *aromatic* because the lone pair of electrons on each ring nitrogen are conjugated as a consequence of being linked via carbonyl carbons at the 2-, 4- and 6-positions.

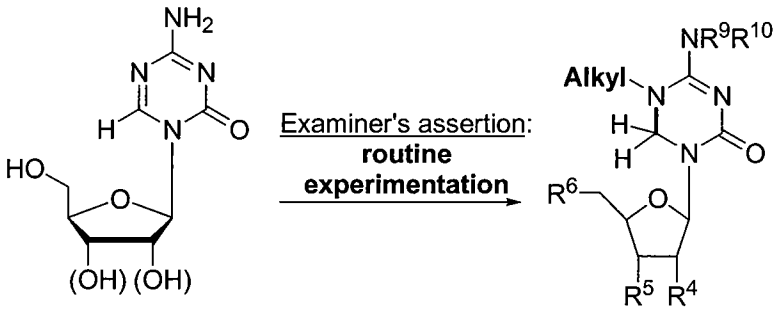


Cytidine **(aromatic)** | Driscoll **(aromatic)** | Wierenga **(aromatic)** | Claim 1 **(non-aromatic)**

In stark contrast to the *aromatic* triazines of Driscoll *et al.* and Wierenga, the triazines of the instant claims are *non-aromatic*. The triazines of the instant claims are unsaturated in the 5,6-position with no carbonyl in the 6-position. Thus, the conjugation at the 6-position necessary for aromaticity that is present in the compounds of both Driscoll *et al.* and Wierenga, is *absent* in the triazines of the instant claims. Accordingly, rather than combining the *saturated* compound of Driscoll *et al.* with the *unsaturated* compound of Wierenga to achieve

the *partially unsaturated* compounds of the instant invention, the Examiner is actually combining the *aromatic* compound of Driscoll *et al.* with the *aromatic* compound of Wierenga to arrive at the *non-aromatic* compounds of the instant invention.

Driscoll *et al.* discloses nucleotides with a 1,3,5-triazine that is *aromatic* as a result of being *fully saturated*, and that is *unsubstituted* at the 5-position. According to the Examiner's assertion, **routine experimentation** with the nucleotides of Driscoll *et al.* would lead one of skill in the art to the *non-aromatic, partially unsaturated* triazines of the instant invention being *substituted* at the 5-position. Applicants respectfully submit that such differences between the triazines of Driscoll *et al.* and the triazines of the instant invention lead to unexpected results, thus making the instant claims not obvious in view of Driscoll *et al.*

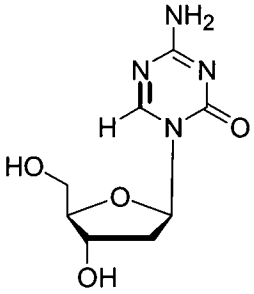


Driscoll
(aromatic)

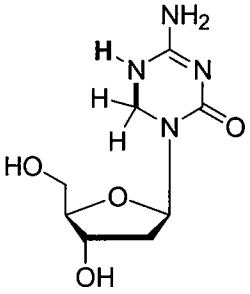
Claim 1
(non-aromatic)

For example, Figure 4 of the instant application shows anti-viral activity of the *aromatic* nucleoside 5-Aza-dC and the *non-aromatic* nucleosides DHAdC and 5-Me-DHAdC. As shown in the structures below, 5-Aza-dC is an *aromatic* triazine with *no substitution* at the 5 position. The *non-aromatic* triazines, DHAdC and 5-Me-DHAdC, however, have only unsaturation at the 3,4-position, and are *substituted* at the 5-position with either hydrogen (DHAdC) or methyl (5-Me-DHAdC). Accordingly, the only differences between the aromatic nucleoside 5-Aza-dC and non-aromatic nucleosides DHAdC and 5-Me-DHAdC, is the saturation at the 5,6-position, and that as a result of the 5,6-saturation in the non-aromatic nucleosides, the 5-position is available for substitution.

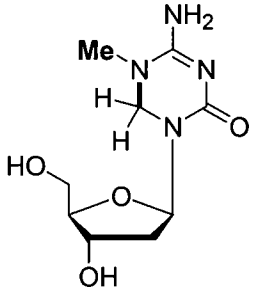
Turning to Figure 4 (reproduced below for the Examiner's convenience and in the accompanying declaration by Dmitri Sergueev ("the Sergueev declaration")), the inhibition profile for the *aromatic* nucleoside 5-Aza-dC shows a steadily increasing inhibition up to 80%, above which the inhibition profile levels off and asymptotically approaches 100% inhibition. Despite the seemingly minor differences between 5-Aza-dC and DHAdC and 5-Me-DHAdC, the inhibition profiles for the *non-aromatic* nucleosides DHAdC and 5-Me-DHAdC show a much different profile. The inhibition profiles for the non-aromatic nucleosides remain relatively low (below 40% inhibition) until a critical concentration is reached, at which point the percent inhibition increases steadily to 100%, with no asymptotic approach to 100% inhibition. Thus, despite the seemingly minor differences between the *aromatic* nucleoside 5-Aza-dC and the *non-aromatic* nucleosides DHAdC and 5-Me-DHAdC, the change from an *aromatic* triazine to a *non-aromatic* triazine results in surprisingly different inhibition profiles.



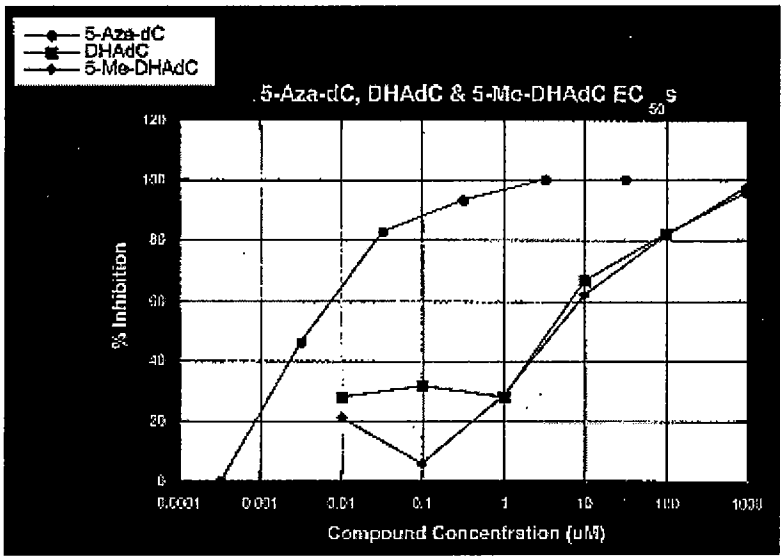
5-Aza-dC
(aromatic)



DHAdC
(non-aromatic)



5-Me-DHAdC
(non-aromatic)

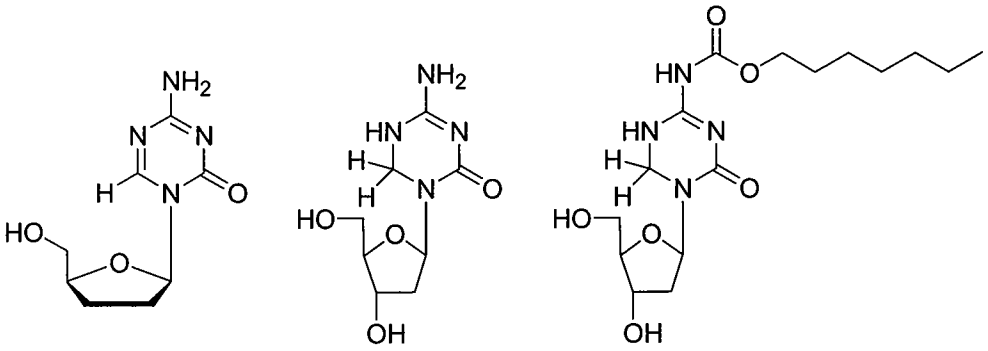


The effect on aromatic vs. non-aromatic triazine is also exemplified by the toxicity data provided in the Sergueev declaration, showing toxicity levels for non-aromatic triazines KP-1212 and KP-1461 versus the aromatic triazine ddC (dideoxy cytidine).

The toxicity levels for the compounds were determined by examining the inhibition of mtDNA synthesis in mammalian cells (Feng et al., 2001), specifically by analyzing lactate and mtDNA production in drug-treated CEM cells.

The lactic acid concentrations in the figure below of the Sergueev declaration are shown as a percentage of the non-treated control. Lactic acid concentration correlates to toxicity, with higher lactic acid concentration equaling higher toxicity levels of the compound. The lactic

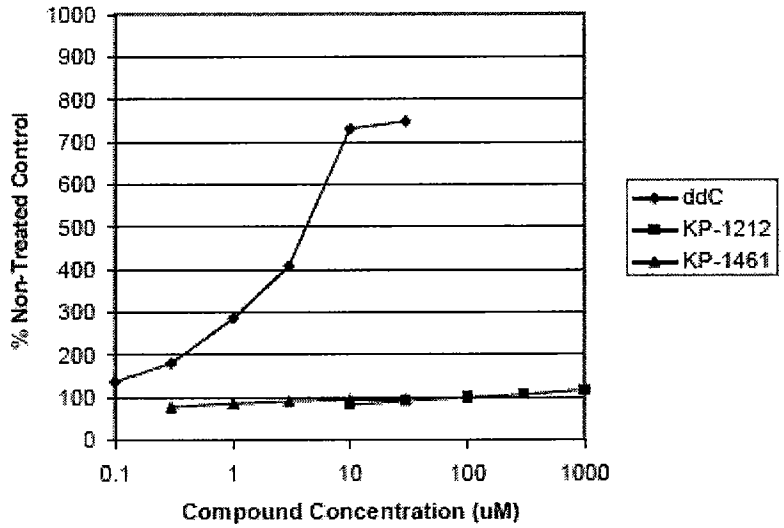
acid concentration for the non-aromatic KP-1212 and KP-1461 show lactic acid concentration at about the levels for the non-treated control. As the lactic acid concentration correlates to toxicity, this demonstrates that the toxicity for KP-1212 and KP-1461 is about the same as that for the non-treated control.



ddC
(aromatic)

KP-1212
(non-aromatic)

KP-1461
(non-aromatic)



The lactic acid concentration for the aromatic ddC shows lactic acid concentration as much as 700% higher than that of the non-treated control. Thus, as stated in the Sergueev declaration, the lactic acid concentration correlates to toxicity, demonstrating that the toxicity for the aromatic ddC is several times higher than for the non-treated control. The Sergueev declaration further states that this data also demonstrates that modification of the triazine from aromatic to non-aromatic has a significant impact on the properties of the compound.

The data provided in the Sergueev declaration in the Figure 4 inhibition profiles and the toxicity data, demonstrate that the aromaticity of the triazine ring plays a not insignificant role in the properties and function of the nucleosides of the present invention. Accordingly, Applicant respectfully submit that one of skill in the art, starting from the *aromatic* triazines of Driscoll *et al.*, would not arrive at the *non-aromatic* triazines of the present invention through **routine experimentation**. As Figure 4 of the instant application demonstrates, replacing the *aromatic* triazine with a *non-aromatic* triazine surprisingly results in noticeably different inhibition profiles and toxicity levels.

Applicants respectfully submit that the combination of Wierenga and Driscoll *et al.* fail to disclose or suggest all the limitations of the claims, as both references fail to teach or suggest a *non-aromatic* triazine. In addition, the teachings of Meyer *et al.* do not provide the failings of Wierenga and Driscoll *et al.* as Meyer *et al.* is drawn to peptide linkers for improving oligonucleotide delivery, and is silent as to specific oligonucleotides.

As both Driscoll *et al.* and Wierenga are drawn to *aromatic* triazines, and Meyer *et al.* is drawn to peptide linkers, none of the cited references provides any motivation to start with the compounds of *aromatic* triazines of Wierenga and Driscoll *et al.* and arrive at the *non-aromatic* triazine compounds of the instant invention. Thus, there is no suggestion or motivation provided by the references to combine Wierenga, Driscoll *et al.* and Meyer *et al.* and arrive at the instant invention.

In addition, there is no reasonable expectation of success provided by Wierenga, Driscoll *et al.* and Meyer *et al.* Applicants respectfully submit that a teaching of an *aromatic* triazine having anti-viral activity, as in Driscoll *et al.* and Wierenga, provides no expectation of success that a similar *non-aromatic* triazine will also have anti-viral activity. As Figure 4 demonstrates, the seemingly simple change from an *aromatic* to a *non-aromatic* triazine drastically changes the inhibition profile for the compound. Thus, there is no reasonable expectation of success provided by the references to start with the teachings of Wierenga, Driscoll *et al.* and Meyer *et al.* and arrive at the present invention.

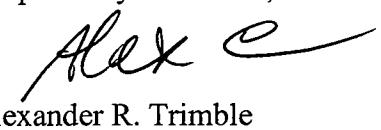
As the combination of Wierenga, Driscoll *et al.* and Meyer *et al.* fail to teach or suggest all the limitations of the instantly amended claims, and there is no suggestion or motivation to combine the references, and there is no reasonable expectation of success, the instantly amended claims are not obvious in view of the cited references. Accordingly, Applicants respectfully request that the Examiner withdraw this aspect of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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Attachments
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